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Management of acute Traumatic Brain Injury in emergency department: Systematic review

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ABSTRACT

Background: Adults who suffer from traumatic brain injury often die from it, become permanently disabled, and incur significant costs to the healthcare system. We aimed to compare the effects of hypertonic sodium and mannitol on intracranial pressure change from baseline, and significant adverse events in patients who have had acute traumatic brain injury. *Method:* The databases of Cochrane, EMBASE, CENTRAL, and PubMed were searched for published articles between 2008 and 2023. We looked for human researches. Bibliographies and recommendations for clinical practice were examined. Studies about the comparison between mannitol and HTS in randomized trials for people with acute traumatic brain injury were collected. *Results*: Six RCTs were included in the systematic review after duplicates and irrelevant studies were eliminated from the chosen publications. We looked at 336 patients in total from the six RCTs. ICP was lowered by 45% of the mean baseline values in patients receiving mannitol infusion for 60 minutes, compared to 35% of the baseline values in the HTS group. Mannitol was just as successful as HTS in lowering ICP, but neither drug was able to enhance brain metabolism. *Conclusion:* MTL was equally successful in lowering ICP as HTS was in the cases of cerebral ischemia, HTS demonstrated better result on cerebral perfusion, which could be helpful.

Keywords: Traumatic brain injury, elevated intracranial pressure, management, systematic review

1. INTRODUCTION

Among young people, traumatic brain injury (TBI) is one of the leading causes of death and long-term impairment (Hinson et al., 2013). According to estimates, around 70 million people have traumatic brain injury (TBI) annually Dewan et al., (2018), making it a major global public health concern that also places a heavy financial burden on the healthcare system. TBI is most frequently caused by falls, violent incidents, and traffic accidents. TBI is caused by more than just the first

physical blow. Secondary injury, defined as biochemical, molecular, and physiological changes following the physical injury, is strongly linked to poor neurological outcomes and patient mortality (Gharizadeh et al., 2022). Research revealed that elevated intracranial pressure (ICP), a frequent TBI consequence, may be linked to subsequent damage in TBI survivors (Corps et al., 2015).

One of the mainstays of treatment for increased ICP in traumatic brain injury (TBI) is hyperosmolar therapy, such as Mannitol and hypertonic saline (HTS) (Vedantam and Gopinath, 2018). Regarding HTS and mannitol in TBI, several new insights have been discovered. For TBI patients, HTS is regarded as standard care (Banks and Furyk, 2008). There are still disagreements on the effectiveness of hyperosmolar components in lowering ICP and improving the general prognosis of TBI patients, despite the fact that numerous studies have examined this topic (Hinson et al., 2013). In terms of reducing mortality or raising ICP, Berger-Pelleiter et al., (2016) comprehensive review showed no discernible difference between HTS and other solutions. Furthermore, Chen et al., (2020) study concluded that HTS is not better than mannitol in TBI patients based on the scant information that was available.

To stop further brain damage in cases of severe traumatic brain injury, it is preferable to treat hypovolemia and hypotension with appropriate resuscitation. Rapid active resuscitation with fluid is necessary for patients with severe TBI who are hypotensive. Care must be taken to avoid raising intracranial pressure and excessive hydrostatic capillary pressure. As a result, lactated Ringers, which is somewhat hypotonic, is regarded as the ideal fluid for volume deficit. It also maintains the intravenous line open for the purpose of giving medication. Because hypertonic saline is positive inotropic and chronotropic and requires less volume at lower capillary hydrostatic pressure, it provides advantages for individuals with brain injuries (Fatima et al., 2019).

2. METHOD

The Preferred Reporting of Systematic Reviews and Meta-Analysis (PRISMA) guidelines were followed in the design and analysis of this systematic review. The following search phrases were combined and used to search PubMed, EMBASE, CENTRAL, and Cochrane databases: Mannitol, hypertonic saline solutions, sodium chloride, traumatic brain injury, osmotic diuretic, head injury, and brain injuries. The search was restricted to human studies and did not consider the publishing language. The reference lists of the papers that were obtained and clinical practice guidelines were also examined. We were able to locate 215 studies after eliminating duplicates. However, only 35 of these were determined to be eligible based only on the abstracts and titles. After the full-text articles were examined, 29 papers were excluded because of unfavorable intervention, study design, and outcomes. Six RCTs were included in the systematic review.

Randomized clinical trials comparing intravenous administration of HTS and mannitol solutions in adult humans with evidence of high ICP related to acute TBI, were the eligibility criteria for study inclusion. Cross-over studies that included a randomized beginning treatment were acceptable for inclusion. Excluded from consideration were studies that solely involved pediatric patients and those with, subarachnoid haemorrhage, or intracranial haemorrhage. Death from all causes was the main result. Morbidity, which is characterised as a functional neurological recovery or disability, was one of the secondary outcomes. To weed out articles that weren't relevant, every reviewer read the abstracts and titles of the papers that detected in search strategy. Additionally, every reviewer attested to each study's eligibility, with disagreements being settled by consensus. To extract the following data, a standardized data collection form was created: Study design and setting; patient characteristics and inclusion criteria; intervention features; key findings; and conclusion.

3. RESULTS

After removing duplicates from the electronic databases, we were able to identify 215 studies; however, only 35 of these were found to be eligible based only on the abstracts and titles. 29 papers were eliminated following an examination of the full-text publications due to the intervention, study design, result, and inappropriate outcome. Consequently, the systematic review contained 6 RCTs (Figure 1). From the six RCTs published by Francony et al., (2008), Cottenceau et al., (2011), Jagannatha et al., (2016), Patil and Gupta, (2019), Huang et al., (2020), we examined a total of 336 patients (Table 1). Since the study by Francony et al., (2008) solely assessed ICP reductions, it was disregarded for the primary result.

While only TBI patients were involved in the other research, some stroke patients included in the Francony et al., (2008) investigation. According to Francony et al., (2008) at 60 minutes into the infusion, ICP was reduced in patients receiving mannitol by 45% of the mean baseline values, as opposed to 35% of the baseline values in the HTS group. Cottenceau et al., (2011) study found that

neither medication was able to improve brain metabolism, and mannitol was effective as HTS in reducing ICP. HTS showed an additional, more pronounced effect on cerebral perfusion in the context of cerebral ischemia, which may be advantageous. As such, the treatment plan must to be customised taking into account the patient's salt level and cerebral hemodynamics.

Regarding mortality Jagannatha et al., (2016) found no change in death rates between the groups after six months, but the HTS group had a tendency towards lower in-hospital mortality. According to Patil and Gupta, (2019) (Table 2) the mean arterial pressure and cerebral perfusion pressure increased when the study medications were given as a bolus. The biggest changes were brought about by the infusion of hypertonic saline, which was followed by 20% mannitol and a mixture of 10% glycerol and 10% mannitol.

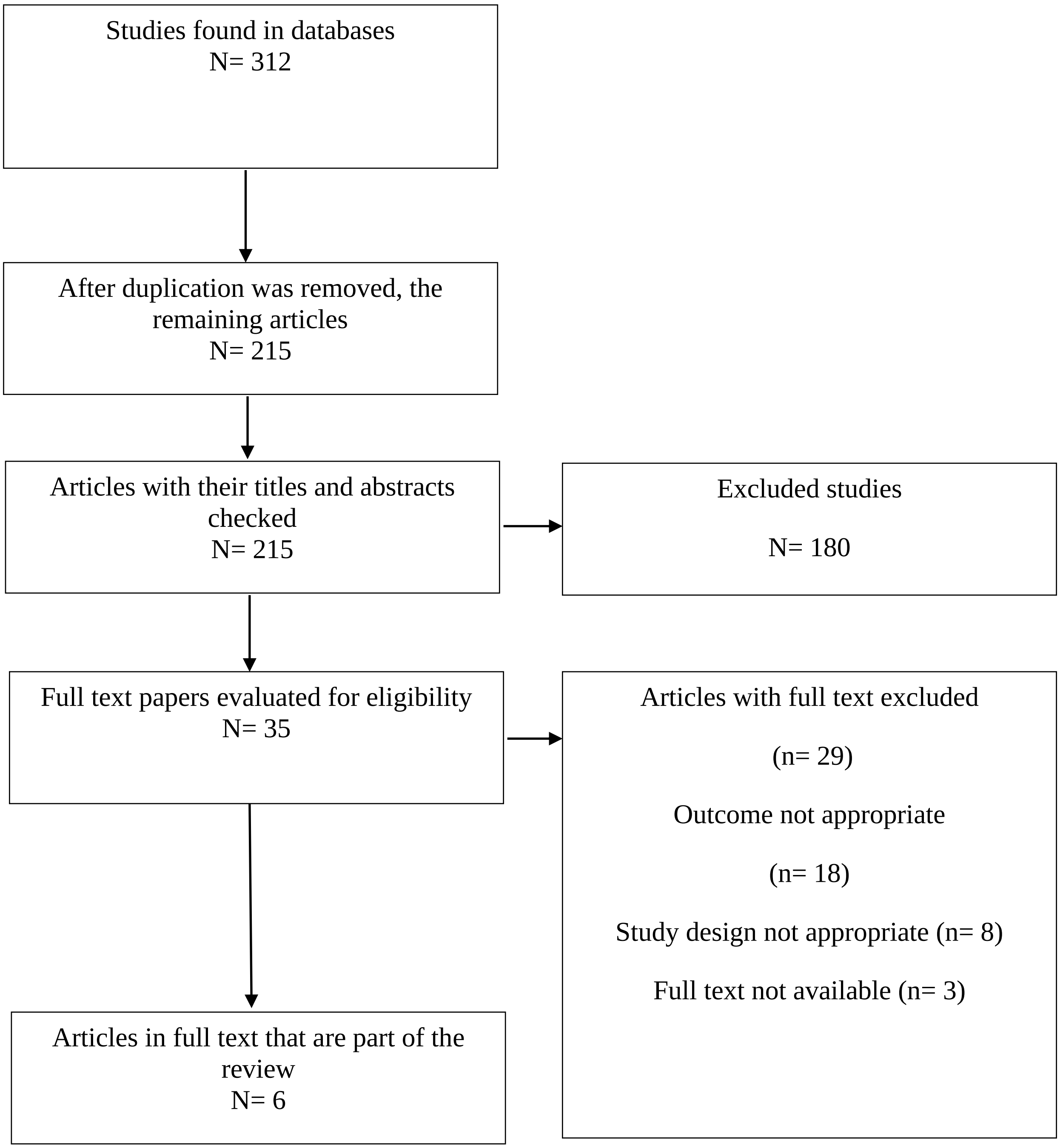

Figure 1 PRISMA consort chart of study selection process

Table 1 Main characteristics of included studies

Citation	Study type	Country	Patients included	Agent used	Inclusion criteria
Francony et al., 2008	Randomized controlled trial	France	20	MTL and HTS	≥18 years old, with a persistently raised ICP of >20 mmHg for more than 10 minutes.
Cottenceau et al., 2011	Randomized controlled trial	France	56	MTL and HTS	TBI with a GCS of ≤ 8 at the time of admission, severe enough to warrant ICP monitoring and mechanical ventilation while under anaesthesia.
Jagannatha et al., 2016	Randomized controlled trial	India	38	MTL and HTS	Patient with severe traumatic brain injury, ages 15 to 70
Patil and Gupta, (2019)	Randomized controlled trial	India	120	MTL, HTS, and mannitol plus glycerol	Older than eighteen, Glasgow Coma Scale less than eight, and high ICP more than 20 mm Hg for longer than five minutes
Huang et al., 2020	Randomized controlled trial	China	83	MTL and HTS	Patients who were at least eighteen years old, had an intra-parenchymal ICP monitor, and had a severe TBI (GCS ≤ 8) upon admission.
-	Randomized controlled trial	USA	22	MTL and HTS	Patient with sever blunt head trauma
Abbreviations; MTL; mannitol, HTS; hypertonic saline					

Table 2 Main findings and conclusion of studies

Citation	Main results	Conclusion
Francony et al., 2008	Throughout the trial, the two therapies decreased ICP consistently and equally. ICP was lowered in patients received MTL by 45% of the mean baseline values at 60 minutes into the infusion, compared to 35% of the baseline values in the HTS group. Lower values of the pulsatility index were seen at various points during the experiment in patients received MTL due to a sustained rise in diastolic blood flow velocity and cerebral perfusion pressure. Following each treatment, there were no appreciable changes in the oxygen tension of brain tissue. The amount of urine produced increased considerably more with MTL than with HTS, although the amount of vascular filling required did not change between the two interventions. Serum salt and chloride levels were increased after 120 minutes of HTS infusion.	Single infusion of 20% MTL reduces intracranial pressure (ICP) just as well as 7.45% HTS. MTL may also improve blood rheology, which has further impacts on brain circulation. For patients with elevated ICP, pretreatment variables such systemic hemodynamics, serum sodium, and brain hemodynamics should be taken into account while deciding between MTL and hypertonic saline.
Cottenceau et al., 2011	While the effects of hypertonic saline and MTL on ICP levels were similar and effective, the effects of HTS on cerebral perfusion pressure, and cerebral blood flow were stronger and lasted longer, and hypertonic saline was associated with better rheological blood characteristics. Furthermore, patients with widespread brain injury seemed to benefit from hypertonic saline influence on ICP more strongly. In contrast, neither solution had any discernible impact on the rates of glucose or oxygen metabolism. Therefore, there was no discernible difference in the two groups' neurological outcomes.	MTL was just as successful as HTS in lowering ICP, despite the fact that neither treatment was able to enhance cerebral metabolism. In the presence of cerebral ischemia, HTS demonstrated an extra, more pronounced effect on cerebral perfusion that may be beneficial. Therefore, the choice of treatment should be individualized based on cerebral hemodynamics and salt level.
Jagannatha et al., 2016	Throughout the course of the investigation, the ICP of the MTL group gradually increased. In the HTS group, there was no such rise. On the sixth day, the HTS group experienced a greater proportion of time when the ICP stayed below 20 mmHg. Compared to the MTL group, the HTS group's inotrope requirement lasted less. When compared to MTL, the slope of the ICP fall in response to a bolus dosage at a particular baseline ICP value was larger with HTS. The HTS group had a tendency to have decreased in-hospital mortality, but no difference in death between the groups after six months. At six months, the groups' dichotomized Glasgow Outcome Scale scores were similar.	The short-term physiological benefits of HTS over MTL did not translate into long-term improvements in cerebral perfusion pressure management mortality of TBI patients.
Patil and Gupta, (2019)	ICP dropped below 15 mm Hg with all three medications. The highest elevation in intracranial pressure (ICP) was observed subsequent to a hypertonic	When an equivalent osmotic load is administered, all three osmotic substances show similar efficacy in

	saline bolus, 10% glycerol combination, and 20% MTL. Following the bolus dosage of the study drugs, there was an increase in mean arterial pressure and cerebral perfusion pressure. The infusion of hypertonic saline caused the greatest alterations, which were then followed by 10% MTL plus 10% glycerol combination and 20% MTL.	lowering ICP; however, hypertonic saline seemed to be more efficient.
Huang et al., 2020	MTL and HTS boluses did not significantly differ in terms of the amount of ICP decrease, the length of the effect, or the time it took to reach the lowest ICP. Both the percentage of effective boluses and the rise in blood sodium were greater for HTS than for MTL. Following osmotherapy, there was an immediate and notable increase in serum osmolality.	Patients with severe traumatic brain injury seem to respond considerably and similarly well to repeated bolus doses of 10% HTS and 20% MTL for treating ICH. Compared to MTL, the percentage of HTS dosages that are effective at reducing ICP may be higher.
-	At the start of treatment, the ICP of HTS patients was noticeably higher than that of the MTL group. The initial cerebral perfusion pressure was the same. Patients receiving HTS experienced a higher mean ICP reduction one hour following the administration of 108 doses of HTS and 102 doses of MTL. HTS elicited more patient responses. The amount of time that the ICP decreased following dosage delivery did not significantly differ between the groups. Following the administration of either drug, no negative effects were noted.	23.4% HTS reduces ICP more effectively than MTL.

4. DISCUSSION

Despite the dearth of randomized controlled trials comparing these two therapies, mannitol and HTS solutions are frequently utilized in the treatment of increased ICP in the case of severe traumatic brain injury. The review found no statistically significant changes in mortality and neurological function outcomes between mannitol and HTS solutions. However, the small number of included trials lacked sufficient power to identify any clinically meaningful differences in these outcomes. HTS therapy has been proposed to have a number of theoretical benefits in TBI cases, including efficient plasma volume maintenance, increased reflection coefficient, dehydration of endothelial cells, which increases erythrocyte deformability and vessel diameter, preservation of the blood brain barrier's integrity and neuronal membrane potentials, and advantageous immune mechanism modulation (Himmelseher, 2007; Ziai et al., 2007; Strandvik, 2009).

The characteristics of the membrane dividing a solution's various compartments and the solution's osmolality determine the solution's osmotic efficacy. This is represented as the osmotic reflection coefficient of a membrane for a specific solute. In order to minimise cerebral edoema and, consequently, intracranial pressure (ICP), an optimal osmotic agent for traumatic brain injury should not cross the blood–brain barrier and instead establish an osmotic gradient that allows water from brain cells to enter the intravascular compartment. However, when compared to mannitol, Jagannatha et al., (2016) study did not show any significant effect of HTS on the sustained control of ICP and CPP over a period of 6 days following severe TBI at equiosmolar dosages.

Additionally, while though it was statistically insignificant, the percentage of time that the ICP was below the threshold level tended to be longer with HTS. This suggests that HTS boluses, as opposed to mannitol, offer a more efficient way to lower ICP when it is elevated. According Patil and Gupta, (2019) study, the three medications that are most effective for treating elevated ICP in patients with severe TBI are HTS 3%, mannitol 10% with glycerol 10%, and mannitol 20%. According to Patil and Gupta, (2019) hyperosmolar solutions have been shown to lower a raised ICP, which makes them useful in emergency scenarios when a patient is rapidly deteriorating and before surgery is performed. In light of that, HTS seemed to function more quickly and efficiently.

Cottenceau et al., (2011) findings demonstrated that HTS had a considerably longer and greater effect than mannitol, and both treatments increased CBF. There is ongoing discussion over the physiological mechanism underlying this CBF enhancement. HTS 22.3% significantly increased CBF by more than 20% in a recent trial conducted in patients who had spontaneous subarachnoid haemorrhage (Al-Rawi et al., 2010). Following admisteration of (hypertonic saline 3% or compination of mannitol 10% and glycerol 10%, or 20% mannitol), there was no change in the hematocrit readings. All three medications increased blood sodium and osmolarity, although HTS 3% increased these parameters far more than the other two medications (Patil and Gupta, 2019). An overabundance of salt and osmolarity can cause hyperchloremic metabolic acidosis, volume overload with heart failure and lung edoema and coagulation problems (Treib et al., 1997).

Consequently, patients with impaired cardiac function should only utilize hypertonic solutions while having close cardiac monitoring. In our study regardless of the concentration or route of administration (continuous drip or bolus), most trials demonstrated a more favorable short-term ICP outcome with HTS. None of the included studies demonstrated unfavorable outcome following administration of HTS bolus. Given the clinical equipoise that determines which hyperosmolar therapy is superior, we have made an effort to give clinicians useful information about the implications and practical factors to take into account when selecting an agent. This information includes suggested clinical settings, administration and availability considerations, and possible safety concerns.

5. CONCLUSION

Though neither treatment was able to improve brain metabolism, MTL was just as effective as HTS in decreasing ICP. HTS showed an additional, more favorable outcome on cerebral perfusion in the context of cerebral ischemia, which may be advantageous. The mortality rate of TBI patients did not improve over time in terms of cerebral perfusion pressure management despite the short-term physiological advantages of HTS over MTL.

Abbreviation

ICP: Intracranial pressure
HTS: Hypertonic saline
MTL: Mannitol
TBI: Traumatic brain injury

Ethical approval

Not applicable

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This study has not received any external funding.

Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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